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Structure and Function of Aquaporins: the Membrane Water Channel Proteins

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Abstract: Aquaporins are integral membrane proteins which are also known as water channel proteins. They aid quick transportation of water across membranes and are important in controlling cell volume and transcellular water passage. Aquaporins are present in organisms, and they vary from archaea and bacteria to plants and animals. They are also found in insects and yeast. Presently, 13 mammalian aquaporins (AQP0 to AQP12) have been cloned and identified in every tissue in the body. These aquaporins are alike in basic structure with monomers containing six transmembrane and two short helical segments that enclose cytoplasmic and extracellular vestibules linked by aqueous pore. They have distinctive structures that define their functions, mode of action, and even their various control methods. Phylogenetic analysis of aquaporin consists of aquaporins, glycerol facilitators, plasma membrane integral proteins of plants, tonoplast integral proteins of plants, nodules of plants, and AQP8s. Aquaporins are structurally related due to their great similarity in their structural regions, mainly in the pore-forming domains, which accounts for the similarity in their transport mechanisms. The water movement by AQPs is controlled by a change in conformation or by modifying the AQP density in the membrane and at the transcriptional and translational levels. Aquaporins are important in several physiological processes and are also linked with several clinical disorders, such as brain edema, loss of vision, and kidney dysfunction.

Keywords: aquaporins; water channel; membrane proteins; transport; permeability.

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1. Introduction

Aquaporins belong to integral membrane proteins that form pores in the biological cell membrane and are essential for facilitating water transport between cells [1]. The importance of water cannot be overemphasized, which results in its abundance in living cells. Aquaporins are also known as water channel proteins. Since the discovery of the first aquaporin (AQP1) in mammals, many aquaporins have been found and classified in microorganisms, plants, and animals [2-4]. Thirteen (13) mammalian Aquaporins, AQP0 to AQP12, have been cloned and identified in every tissue in the body. They differ in size with diverse water permeability. The channel-forming integral protein (CHIP28), known as a major erythrocyte plasma membrane protein, was reported to be the first protein identified with a water transport activity. As the first example of the water channel protein, the nomenclature CHIP28 was changed to AQP1[5].

Aquaporins (AQPs) are known to be water channel proteins that exhibit numerous functional properties in plant growth and development, such as uptake of uncharged solute,

stress response, control of cell volume, and transcellular water passage. Aquaporins conduct water at a rate of 109 molecules per second, which is almost comparable to the free diffusion of water [6].

Aquaporin provides a proteinaceous pathway for water. They are of a similar basic structure, consisting of a narrow aqueous pore that is connected to the cytoplasmic and extracellular vestibules surrounded by aquaporin monomers containing six transmembrane and two short helical segments. The short helical segments have several conserved motifs and Asn-Pro-Ala (NPA) sequences [7].

Mammalian aquaporins are expressed in different organs such as the brain, kidney, lens, lungs, and also in cell types implicated in fluid transport such as eye, gastrointestinal organs, etc. However, it has been reported that cells with no obvious role in fluid transport also expressed aquaporins. Examples of these cells are erythrocytes and some leukocytes, adipocytes, and skeletal muscle. Other cells that express aquaporins include astrocytes, supportive cells, and sensory organs [7]. In plants, aquaporins are known to contribute to a range of physiological processes such as photosynthesis. They are also known to play a role in the pathophysiology in various clinical conditions such as diabetes insipidus and edema and could target therapy in altered water homeostasis diseases [8].

About eleven (11) different aquaporin types are found in different parts of the human body. Multiple water-channel homologs are expressed in the kidney, lung, eye, and brain, which provide an arrangement for water transport in those locations. AQP1, 3, 5, 7, 9, and 10 are expressed in the human skin, but only AQPs of the sweat and sebaceous glands and epidermis are strictly related to skin physiology. AQP5 functions as water secretion in sweat glands[9]. AQP3 is expressed in keratinocytes, and it is important in the transport and metabolism of glycerol in mouse skin epidermis [10].

The digestive system's major function is secretion and absorption, which requires the transport of fluid across cellular membranes[11]. AQP1 is expressed in the digestive system along the apical, basolateral membranes and an endothelial cell which is responsible for transendothelial water transport [12]. Aquaporin 3 is expressed in the epithelial lining [13], while both AQP3 and 4 are expressed in the gastrointestinal tract [14]. AQP8 is expressed in the apical plasma membrane of pancreatic duct cells[15], while AQP9 is found in the liver hepatocytes [16].

Cell membranes' porosity to water and hormones in both the male and female reproductive systems is vital for folliculogenesis [17], spermatogenesis, and sperm osmo-adaptation [18]. AQPs are found to be linked with the pathogenesis of several reproductive disorders such as polycystic ovary syndrome[19].

Aquaporin families in plants are complex and are made up of a great number of genes. For instance, about 35 AQPs are found in *Arabidopsis thaliana*, 34 in *Oryza sativa,*31 in *Zea mays*, etc. [20]. AQPs play a key role in water and solute transport and maintain water homeostasis in response to environmental stresses. The roles of aquaporins in glycerol, boric acid, urea, NH_3, and CO transport via cell membranes are also essential for seed germination, cytoplasm homeostasis, petal and leaf movement, maintenance of cell turgor under various stresses, and fruit ripening [2]. Several uncharged solutes or gases such as urea, ammonia, carbon dioxide (CO_2), hydrogen peroxide (H_2O_2), nitric oxide (NO), etc., are reported to cross the cellular membrane via aquaporin channels [21].

Aquaporins have been characterized into seven subfamilies: small basic intrinsic proteins (SIPs), plasma membrane intrinsic proteins, x-intrinsic proteins, h-intrinsic proteins,

intrinsic glycerol proteins,nodulin-like plasma membrane intrinsic proteins, and tonoplast intrinsic proteins [22, 23].

2. Structure of Aquaporins

Aquaporins are expressed generally throughout the plant and animal kingdoms. They are alike in basic structure, with monomers containing six transmembrane and two short helical segments that enclose cytoplasmic and extracellular vestibules linked by aqueous pore [7]. They have several conserved motifs in their short helical segments as well as NPA sequences. Aquaporin monomers form tetramers in membranes, and each monomer forms functional water more independently. The tetrameric structure is common to all the AQP family. Some aquaporins, such as mammalian AQP4, can further be combined in cell membranes to form assemblies of a supramolecular crystalline structure called orthogonal arrays of particles [7].

The six transmembrane α-helical protein domains in the membrane plane form a barrel-like configuration. The amino and carboxy-terminal domains are responsible for the specific regulation of aquaporin activity. The cytoplasmic loops and the periplasmic loops are made up of two short α-helical domains on the opposite sides of the barrel, which are said to contribute to the water channel's formation. The domains are situated close to each other in the molecule. Each domain is made up of the NPA (Asn-Pro-Ala) motif, which is conserved for all aquaporins [24]. The structure is regarded as the ‘hourglass model’ [25]. The ‘hourglass model’ structure was established as three-dimensional maps of AQP1 through cryoelectron microscopy. The structure showed that aquaporins contain tetrameric subunits placed in parallel, forming a fifth pore in the tetramer center [26]. When incorporated into the membrane, aquaporins generate homotetramers [27]. The tetramer's assemblage is essential for appropriate folding and stability of protein, sorting, and posttranslational modifications of proteins. Each of the four subunits produces an independent water channel in the complex, whereas the pore is oriented along the tetramer axis [28, 29].The quaternary structure of the water channel is at variance in stability for various phylogenetic clusters of aquaporins. The tetramers of aquaporins with glycerol specificity are less stable [30].

The passage of water along the pore in a thermodynamically favorable condition is provided by forming new hydrogen bonds between the water molecule and aquaporin atoms. The binding to the protein occurs due to the oxygen atoms of the peptide groups from a number of sequential amino-acid residues [31]. The chains have both cytoplasmic and external surfaces which project towards the pore center. The chains are formed by amino acids of the loops containing two short α-helical domains. The protein molecule has at the center two NPA motifs with closely positioned asparagine residues that form the middle pore region. The amide groups of these residues also form hydrophilic areas over the channel surface. The transport of water molecules from one asparagine residue to another causes a release of molecules from a continuous hydrogen bond system formed as a result of water movement along the water pore [32].

3. Family of Aquaporins

Aquaporins are made up of a family of water-transporting membrane proteins. Members of the AQP family are divided into two subfamilies based on their permeability characteristics:

(i) Classic AQPs (water selective) which conduct water exclusively;

(ii) Aquaglyceroporins possess the extended ability to conduct small linear carbohydrates, in particular, glycerol, a metabolic intermediate [33];

Based on the functions of aquaporins, they are classified into three subfamilies:

(a) Those that are selectively permeable for water. They are also known as orthodox aquaporins, which includes AQP1, 2, 4 and 5;

(b)Those that are permeable to water as well as to glycerol, urea, and/or other small solutes; They are also known as aquaglyceroporins which include AQP3, 7, 9 and 10; and

(c) Unorthodox aquaporins, which include AQP6, 8, 11, and 12;

Thirteen (13) aquaporins subtypes have been identified recently, and their distribution in various tissues is linked to their functional roles in water-transporting [34]. More so, aquaporins may also be classified into five categories; classical aquaporins, unorthodox aquaporins, AQP8- type aquaammoniaporins, plasma membrane intrinsic, and aquaglyceroporins, according to the phylogenetic tree or phylogenetic topology as inferred from Bayesian inference.

3.1. Aquaporin 0.

The mRNA encoding AQP0 was initially identified in 1984 [35], and it was believed to be an aqueous channel and/or a gap junctional protein. It was referred to as MIP- major intrinsic protein of the lens. However, following the discovery of AQP1 and developing the functional assays for water transporters, it was renamed AQP0 [36]. This channel transports water at a slower rate than that of AQP1 [37], and in addition to facilitating water, AQP0 has been reported to play a role in the cell-to-cell adhesion of the lens fiber. Studies have shown that human individuals with mutations in AQP0 suffer from cataracts, a symptom ranging from cloudy vision to blindness [38].

3.2. Aquaporin 1.

AQP1 is the most studied aquaporins. It was reported as the first protein for which water transport was measured, and a high-resolution structure was determined [39]. Studies have identified a clear gating mechanism of action of AQP1 and that alteration of osmotic conditions could induce a reversible protein kinase C (PKC) dependent change in the membrane localization of AQP1 [40], which suggests a regulatory mechanism by trafficking. The protein is found in many different tissues in the body, including red blood cells, kidneys, and lungs. Mice and humans lacking AQP1 have shown to have urinary concentration deficiency during water deprivation [41].

3.3. Aquaporin 2.

AQP2 was discovered shortly after AQP1. It was found in the renal collecting duct and hence called the water channel of the collecting duct (WCH-CD) [42]. The trafficking of AQP2 is one of the most studied aquaporin regulation mechanisms. Vasopressin triggers cAMP signaling, leading to activation of protein kinase A, which phosphorylates AQP2 resulting in translocation to the apical plasma membrane [43]. A mutation in AQP2 causes nephrogenic diabetes insipidus [44], and mice with mutations in this gene show severe urine concentration defects [45].

3.4. Aquaporin 3.

AQP3 was first identified in the basolateral membrane of the collecting duct in the kidney[46]. It was named glycerol intrinsic protein (GLIP) or AQP3.In addition to water transportation, AQP3 could also transport glycerol and urea. Aquaglyceroporin AQP3 was found to be aberrantly expressed in various human cancers, including human skin cell carcinomas and melanoma [47]. It is abundant in keratinocytes in the basal layer of the epidermis in human skin [48]. Low pH and nickel concentrations could bring about inhibition of AQP3 [49].AQP2 is reported to be down-regulated in AQP3 null mice, causing deficiency in urine concentration and nephrogenic diabetes insipidus [50].

3.5. Aquaporin 4.

AQP4 was first cloned from rat lung [51] and rat brain [52] and was named mercurial insensitive water channel (MIWC) due to the lack of mercury inhibition. Isoforms of AQP4 were identified in the brain and were shown to possess several amino acids and are reported to transport water at higher rates [53]. There are two human isoforms; AQP4-M, a full-length protein, and hAQP4-M23, which is the shorter, lacking the first 22 amino acids. [54]. AQP4 plays a major role in the control of water balance in the brain. A high-resolution structure of truncated hAQP4 has also been reported with some differences in the interaction with waters along the channel, as compared to other water-selective AQPs [55].

3.6. Aquaporin 5.

Aquaporin 5 is one of three human aquaporins with a known structure [56]. AQP5 was first identified from a rat salivary gland, sweat glands, eyes, and lungs [57]. In the lungs, AQP5 is found in the submucosal glands' secretory cells [58, 59]. Studies have shown reduced secretion of AQP5 in the sweat gland[60]. However, this observation is contrary to another report[61]. Human AQP5 was found in salivary glands' apical membrane, but it was primarily located in patients' basal membranes with Sjögren's syndrome [62]. Defective hAQP5 trafficking causes dry mouth and dry eyes, typical symptoms of patients suffering from Sjögren's syndrome. Moreover, AQP5 null mice have a major reduction in saliva production [63]. In contrast, reports are indicating that the tear secretion is independent of any aquaporin [64].

3.7. Aquaporin 6.

AQP6 was first cloned from rat kidneys and was initially referred to as water channel 3(WCH3). AQP6 was found to aid the transport of anions. A human AQP6 variant with a slightly different sequence was also identified and referred to as hKID [46]. In contrast to other aquaporins located in the kidney, AQP6 was found to be located in intracellular vesicles, making it less likely to be involved in the reabsorption of water. AQP6 functions as an acid-base regulator, with pH being the activating mechanism [65].

3.8. Aquaporin 7.

AQP7 was first cloned from rat testis [66] and was found to transport glycerol through aquaglyceroporin with a high affinity for glycerol [67-69]. However, in humans, it was first detected in adipose tissue [70], giving it the initial name AQP adipose (AQPap). The role in

this tissue is to provide the glycerol needed for gluconeogenesis [71]. AQP7 has also been found to reabsorb glycerol in the kidney [72].

3.9. Aquaporin 8.

AQP8 was found in different tissues such as the colon, placenta, liver, heart [73], testis [66], and pancreas [74]. In rat liver cells, AQP8 was observed to be trafficked from intracellular vesicles to the plasma membrane in response to cAMP [75].

3.10. Aquaporin 9.

AQP9 was first identified in human white blood cells, where it was found to transport water and urea but not glycerol [76]. Roles of AQP9 include facilitating glycerol uptake in the liver [77] and acting as a glucose metabolite channel in the brain [78].

3.11. Aquaporin 10.

AQP10 is an aquaglyceroporin expressed only in the human gastrointestinal tract but not in the mouse small intestine, where it has been demonstrated to be a pseudogene. AQP10 has been reported to transport water, glycerol, and urea when expressed in *Xenopus* oocytes [79].

3.12. Aquaporin 11.

AQP11 is a 271-amino-acid protein in which the second NPA motifs are conserved, but the first motif is substituted by NPC(Asn-Pro-Cys) in both mice and humans [34].In immunohistochemical studies, AQP11 has been found in intracellular compartments of proximal kidney tubes [80].

3.13. Aquaporin 12.

AQP12 was found by searching for homologs to AQP11. The protein was localized intracellularly in the pancreas. AQP-12 is a 290- or 295-amino-acid aquaporin that is closely related to AQP-8 in humans and to AQP-0 and AQP-6in mice [81]. The first NPA motif in AQP-12 is substituted by an NPT (Asn-Pro-Thr) motif in both species.

4. Mechanism of Action of Aquaporin

A similar transport mechanism can be assumed for all aquaporins because they are structurally related and have highly similar consensus regions, most especially in the pore-forming domains. The hydrophobic domain has been suggested to be involved in substrate specificity and/or size restriction. The aquaporin monomer's pathway is lined with conserved hydrophobic residues that permit rapid water transport in the form of a single-file hydrogen-bonded chain of water molecules[30].

The pore has two constriction sites: an aromatic region which is made up of a conserved arginine residue (Arg195) forms the narrowest part of the pore[82], and the highly conserved NPA motifs form a second filter, where single water molecules interact with the two asparagine side chains[30]. The dipolar water molecule rotates 180 degrees during the passage via the pore. The two filter regions build up electrostatic barriers, which prevent the permeation of protons as a result of direct interaction between water molecules and the NPA motifs [82].

The water permeability and selectivity of aquaporins vary considerably. The water permeabilities for human aquaporins have been estimated to be between 0.25 x 10^{-14} cm^3/sec for AQP0 and 24 x 10^{-14} cm^3/sec for AQP4 [83].

Plant plasma-membrane aquaporins have aquaporin activity at different levels [84]. Plasma membrane intrinsic proteins (PIP1 and PIP2) isoforms from maize due to coexpression and heteromerization induced an increase in permeability than the expression of single isoforms [85]. Heteromerization seems to be important in heterologous expression systems and the plant, as was revealed by analysis of PIP1 and PIP2 antisense Arabidopsis plants[86].

The mechanism by which aquaglyceroporins promote glycerol transport has been investigated for the *E. coli* glycerol facilitator GlpF [87]. It was reported that the protein also has conserved NPA motifs at similar positions to those in the water-selective aquaporins, but aromatic amino acids achieve the preference for glycerol at the periplasmic side [87].

5. Regulation of Aquaporins

AQPs mediate the bidirectional water flow driven by an osmotic gradient. The transport of water-mediated by AQPs is regulated either by gating, conformational change, or altering the AQP density in a particular membrane. The trafficking of AQPs is regulated at the transcriptional and/or translational level and involves shuttles of AQPs between intracellular storage vesicles and the target membrane. The regulation of AQPs, either through gating or trafficking, allow for rapid and specific regulation in a tissue-dependent manner. Another relatively long-term regulation by which increased/decreased protein abundance of AQPs is affected is by systemic hormones (e.g., vasopressin, insulin, angiotensin II), local molecules (e.g., purine, prostaglandins, bradykinin, dopamine, and other common microenvironment signals, including pH, divalent cation concentrations and osmolality [88].

The regulations of AQPs are often associated with certain physiological or pathophysiological conditions. The cellular functions of aquaporins are regulated by posttranslational modifications, e.g., phosphorylation, ubiquitination, glycosylation, subcellular distribution, degradation, and protein interactions [89]. AQPs are consequently expressed in bronchopulmonary tissues and are regulated to facilitate transcellular water transport [90].

In plants and yeast, the plasma membrane-localized AQPs are gated in response to environmental stress [50]. In mammals, gating regulates the water permeability of AQP0 in a pH-dependent and Ca^{2+}-calmodulin-dependent manner. The water transport via AQP0 is regulated by C-terminal cleavage, pH, and Ca^{2+}/calmodulin (CaM).

6. Regulation of Different Aquaporin Activity

Cyclic nucleotide and protein kinase pathways are the two regulatory mechanisms currently proposed to be involved in the activation of AQP1 channel activity. Cyclic nucleotides such as cAMP are known for their role as second messengers in both hormone and ion-channel signaling in eukaryotic cells either directly or via activation of protein kinases and subsequent phosphorylation of substrate proteins. It has been demonstrated that cAMP increased the membrane permeability of water in *Xenopus oocytes* injected with AQP1 [91].

AQP2 is regulated by trafficking between intracellular storage vesicles and the apical membrane, a process that is tightly controlled by the pituitary hormone vasopressin. The signaling transduction pathways ensuing in the AQP2 trafficking to the apical plasma

membrane of the collecting duct principal cells and the changes to AQP2 abundance in times of water-balance disorders have been studied extensively. AQP2 plays a key role in short-term regulation and long-term adaptation to collect duct water permeability [92].

Short-term regulation is the process by which vasopressin quickly increases water permeability of the collecting duct principal cells by stimulating vasopressin 2receptor (V2R) in the basolateral plasma membrane and translocation of AQP2 from intracellular vesicles to the apical plasma membrane [93].

Long-term adaptation of collecting duct water permeability ensue when circulating vasopressin levels are raised over a period of hours to days, leading to an increase in AQP2 abundance per cell in the collecting ducts[94]. Studies have also demonstrated that ubiquitination and subsequent proteasomal and/or lysosomal degradation of AQP2 could play a critical role in regulating AQP2 abundance [95].

The expression of AQP3 could be regulated by the Ah Receptor (AhR), which, in turn, is activated by numerous exogenous and endogenous ligands. AhRis triggered in response to environmental pollutants, and it has been shown to regulate several cellular processes, including cell migration and plasticity [96, 97].

AQP5 expression has been reported to be regulated by osmolality. It was suggested that an osmotic gradient between a cell and its environment is involved in regulating AQP5 expression [81]. AQP5 expression is reported to be regulated by a cyclic AMP/protein kinase A (cAMP/PKA)-dependent pathway [98].

7. Functions of Aquaporins

Most aquaporins' primary function is to transport water across cell membranes in response to osmotic gradients created by active solute transport. Non-transporting functions for some aquaporins have also been suggested, such as cell-cell adhesion, membrane polarization, and regulation of interacting proteins, such as ion channels [7]. In injury conditions, AQPs enhance short-term vulnerability to pathological volume changes and promote edema formation [99].

AQPs have various known physiological roles; urine concentration in kidney tubules, epithelial fluid secretion of saliva, cerebrospinal fluid, and aqueous humor production, cell migration required for angiogenesis and wound healing, regulation of brain water homeostasis, neural signal transduction, skin moisturization, cell proliferation in wound healing and fat metabolism.

AQPs function as components of the vital cellular apparatus to maintain the physiological homeostasis of the musculoskeletal system. Several AQP family members are expressed within the epididymis of the male reproductive tract [100]. They are localized to the epithelial layer and are thought to play an important role in transepithelial water transport and sperm concentration [100]. Evidence has shown that AQPs play an important role in the maintenance of the structure and function of sperm and thus male fertility[101].

AQP0 is the protein in the eye lens's fiber cells, where it is required for homeostasis and transparency of the lens [102-106]. AQP1 water channel blockers, as earlier reported, could be potent anti-brain tumor edema agents [107]. AQP1 is expressed in choroid plexus epithelium and may be important in forming cerebrospinal fluid [108]. AQP2 is the vasopressin-regulated water-channel protein found at the connecting tubule and collecting duct and plays a crucial role in urine concentration and body-water homeostasis[109]. AQP3 is the most abundant skin aquaglyceroporin, facilitates water and glycerol transport, and plays a major role in the

hydration of mammalian skin epidermis and proliferation and differentiation of keratinocytes [110]. One of the mechanisms proposed to explain AQP3 participation in tumor growth and spread is the ability to transport H_2O_2, thereby modulating oxidative stress and triggering signaling cascades responsible for cell proliferation and migration [111, 112]. AQP3 may mediate the reabsorption of water from feces by transporting it from the lumen across the endothelial layer into the blood vessels via AQP1 [113].

AQP4 is involved in diverse functions such as regulation of extracellular space volume, potassium buffering, cerebrospinal fluid circulation, waste clearance, neuroinflammation, osmosensation, cell migration, and Ca^{2+} signaling [114]. AQP4 regulates transcellular water flow in cerebral edema [101].AQP5 is expressed in glandular epithelia, alveolar epithelium, and secretory glands, where it is involved in the generation of saliva, tears, and pulmonary secretions. AQP5 is also found at the plasma membrane in the stratum granulosum and reported to play a role in transcellular water homeostasis in the skin [115].

AQP3 and AQP5 were found to be abnormally expressed in quite a number of human tumors and have been considered potential therapeutic targets and biomarkers with prognostic value[116].

AQP6 enables the transport of urea, glycerol, nitrate [117], and AQP7 facilitates water, glycerol, urea, ammonia, and arsenite [107].

AQP8 has been reported to facilitate hydrogen peroxide diffusion across mitochondrial membranes in situations when reactive oxygen species are generated [39]. AQP9 is expressed at the sinusoidal plasma membrane of hepatocytes [118], where it serves as a conduit for the uptake of ammonia and mediates the efflux of newly synthesized urea. AQP9 could also function as a glycerol channel to facilitate glycerol uptake in the liver. AQP10 and AQP7 are important for maintaining normal or low glycerol contents inside the adipocyte, thus protecting humans from obesity [119]. AQP12 functions in controlling the proper secretion of pancreatic fluid following rapid and intense stimulation.

8. Conclusions

Since the first aquaporin description, much information on the physiological significance of these channel proteins has accumulated. Water channels have been identified in almost every living organism, from plants to animals, from prokaryotes to eukaryotes, including humans. Water regulation is crucially important for every cell and, therefore, for all life forms on earth. Structural features, such as the right-handed helical bundle and the mostly hydrophobic pore, were revealed by electron crystallography. While all AQPs share the same basic fold, the subtle differences between the different AQPsprovided most of the insights. Structural and dynamic information on the atomic scale is a prerequisite to understanding the function of a channel, and this information could become the basis for designing novel therapeutics for various diseases related to water balance perturbation.

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Conflicts of Interest

The authors declare no conflict of interest.

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